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| EXAMINER | |
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| ROONEY, NORA MAUREEN | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/651,136 | SIPKA ET AL. | |
| | Examiner | Art Unit | |
| | NORA M. ROONEY | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *27 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-3,5-18 and 20-25* is/are pending in the application.

4a) Of the above claim(s) *6-9,11,12 and 14-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5, 10, 13, 17-18, 22-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 06/27/2008 has been entered.

2. Claims 1-3 and 5-18 and 20-25 are pending.

3. Claims 6-9, 11-12, 14-16 and 20-21 stand withdrawn from further consideration pursuant to 37 C.F.R. 1.142(b) as being drawn to a nonelected species.

4. Claims 1-3, 5, 10, 13, 17-18 and 22-25 are currently under examination as they read on a process for inhibiting allergic disease in humans by aerosol administration.

***Claim Rejections - 35 USC § 103***

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-3, 5, 10, 13, 17-18 and 22-25 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Cochran et al. (PTO-892 mailed on 01/29/2008 , Reference U) in view of Previte et al. (PTO-892 mailed on 05/16/2007, Reference W) for the same reasons as set forth in the Office Action mailed on 01/29/2008.

Cochran et al. teaches:

A process for decreasing development of allergic asthma (OVA induced asthma) comprising exposing an infant, neonatal or immature mammal maturing in an overly sterile environment shortly after birth (2-3 week old laboratory mice) to lipopolysaccharide derived from extracted bacterial endotoxin (E.coli LPS) by administering an aerosol spray composition of the mammal to a living environment/space (saline and air during nasal aspiration) during maturation of the mammal (at 2-3 weeks) (In particular, abstract, page 268, right column, whole document).

Cochran et al. also teaches that "recent studies raised the intriguing hypothesis that exposure to LPS may interact with the immune system in early life and produce a protective environment against the development of asthma and atopy. Despite the potential importance of this phenomenon in the pathogenesis of childhood asthma, only recently have animal models been used to study the interactions between endotoxin and allergic responses as a function of age" and "patients become symptomatic in their first 5 years of life" (In particular, page 268, left column).

The claimed invention differs from the prior art by the recitations of:

"irradiation detoxified lipopolysaccharide" in claims 1-3, 5, 10, 13, 17-18, 22-25;

"wherein exposure comprises at least weekly administration during maturation of the mammal" of claim 1;

"wherein the irradiation-detoxified lipopolysaccharide is detoxified by exposure of the endotoxin to irradiation at a level of from about 25 to about 150 kGy" in claim 2;

"wherein the irradiation changes the structure of the endotoxin while maintaining its Th1 stimulatory positive immune effect in the resulting irradiation-detoxified lipopolysaccharide" in claim 3;

"wherein the mammal is a human and during maturation is between 1 month and 2 years of age" of claim 13;

""during maturation" is throughout the maturing life cycle of the mammal" of claim 17;

"wherein administration is on a daily basis" of claim 18;

"wherein the mammal is a human infant and exposure comprises at least weekly administration from 1 month to 2 years of age" of claim 24 ; and

exposing a "human of up to about 2 years of age" and "wherein exposure comprises administration on an at least weekly basis of an aerosol spray composition comprising the irraditation-detoxified lipopolysaccharide at a concentration of 5-15 μg/ml" in claim 25.

Previte et al. teaches the detoxification of isolated LPS of S. typhimurium, S. enteritidis and E. coli using 4, 4.8 and 4.5 Mrad (about 25 to about 150 kGy) ionizing radiation. The detoxification eliminates lethality induced by its lethal determinants (changes the structure), while retainining antigenticity (maintaining its Th1 stimulatory effect ) and pyrogenicity (In particular, abstract, whole document).

The functional limitations of The recitation of "operable to stimulate the Th1 arm of the human's immune system" of claims 1 and 22; and "operable to stimulate the Th1 arm of the human's immune system while reducing interleukin 1 (IL-1) stimulation caused by the native form of the lipopolysaccharide derived from extracted bacterial endotoxin" of claim 25; and "by restoring normal immune system development" in claim 22 are inherent properties of the reference irradiation-detoxified lipopolysaccharide. Where the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may be an inherent characteristic of the prior art, it has the authority to require the

applicant to prove that the subject matter shown in the prior art does not possess the characteristics relied on. In re Schreiber, 44 USPQ2d 1429 (Fed. Cir. 1997).

It is noted that the specification does not provide a limiting definition for the term "living environment" and "living space" Therefore, the terms apply to all things that are in a "living environment" or "living space" including saline and air.

Claims 1-3, 5, 10, 13, 17-19, 22-25 are included because it would be conventional and within the preview of those skilled in the art to identify and determine the optimal modes, doses and frequency of administration. It has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to practice the process taught by Cochran et al in humans of 1 month to 2 years of age and during the maturing life cycle of the mammal. Cochran et al. suggests performing the process for decreasing development of allergic asthma in young children under 5 years of age implicitly.

One of ordinary skill in the art would have been motivated to use the irradiation detoxified lipopolysaccharide of Previte et al. in process for decreasing allergic asthma of

Cochran et al. because the process should be safe and without toxic effects for use in infants and children. Previte et al. teaches that LPS can be irradiation-detoxified of its lethal determinants while still retaining antigenicity and pyrogenicity. Therefore, it is obvious to use a safer, less toxic form of LPS in neonatal or immature mammals to decrease allergic asthma.

From the reference teachings, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

Applicant's arguments filed on 06/27/2008 have been fully considered, but are not found persuasive.

Applicant argues:

"The claims under rejection include three independent claims. Independent claim 1 is directed to a process for decreasing development of allergic asthma. The process comprises exposing a neonatal or immature mammal to irradiation-detoxified lipopolysaccharide (IR- LPS) derived from extracted bacterial endotoxin and operable to stimulate the Th 1 arm of the mammal's immune system, wherein exposure comprises *at least weekly* administration during maturation of the mammal via application of the IR-LPS to a respiratory environment of the mammal. Independent claim 22 is also directed to a process for decreasing development of allergic asthma in a mammal maturing in an overly sterile environment by restoring normal immune system development, the process comprising exposing a neonatal or immature mammal to irradiation-detoxified lipopolysaccharide derived from extracted *E. coli* bacteria endotoxin and operable to stimulate the Th 1 arm of the mammal's immune system, wherein exposure occurs via administration of the IR-LPS during maturation of the mammal. According to independent claim 25, the process for decreasing development of allergic asthma comprises exposing a neonatal or immature human of up to about 2 years of age to irradiation-detoxified lipopolysaccharide derived from extracted bacterial endotoxin and operable to stimulate the Th 1 arm of the human's immune system while reducing interleukin I(IL-1) stimulation caused by the native form of the lipopolysaccharide derived from extracted bacterial endotoxin, wherein exposure comprises administration on an at least weekly basis of an aerosol spray composition comprising the irradiation-detoxified lipopolysaccharide at a concentration of 5-15 gg/ml.

Applicants emphatically submit that the Cochran disclosure is no more than basic science without any established utility, without potential for the utility enabled by the present invention, and without a mere suggestion of the impact on development of the adaptive immune system by IR-LPS versus LPS, or with respect to the particular efficacy of IR-LPS over LPS in decreasing development of allergic asthma.

Cochran is directed to a study intended to address "the recent hypothesis that bacterial LPS may interact with the immune system in early life to produce a protective environment." Aside from a statement of the thesis, there is no real support and certainly no disclosure of a relevant method. The Cochran study was "designed to characterize the airway responses to LPS in developing mice," yet Cochran notes the insufficiency of the generated data in supporting the thesis, noting in particular the lack of disruption to the Th-1/Th-2 balance and stating that much remains to be investigated.

The Examiner insists that the steps of Cochran are equivalent in essential terms to the steps of the instantly inventive methods. Applicants submit that the difference between the basic science protocol disclosed by Cochran and the present inventive processes are many, many inventive steps apart in both sophistication, real world utility, and demonstrative evidence of an unpredicted and heretofore unknown differential impact of IR-LPS over LPS. This unrecognized impact forms the basis for many of the unpredicted advantages of the present invention, including the ability to decrease development of allergic asthma by treatment of the environment without impacting allergic sensitivities of others living in proximity to the treated subject.

Cochran anesthetizes 2 week old mice and directly applies a saline solution of LPS intranasally, whereas according to the present inventive processes a mist containing IR-LPS is applied to the environment (typically to a living space) of an immature mammal. Application in accordance with the present methods is at least weekly for some period of time during the maturation life cycle of the mammal. This ensures a nearly continual exposure to the IR-LPS across this time frame. In summary form, substantial differences between the method of Cochran and the instant inventive methods include:

Further, these express "step" element differences confer substantial and patentable differences in the functioning of the respective methods. Cochran discloses a resulting airway hyperresponsiveness that results in a transient decrease in airway response to a single known allergen, methacholine, with no discernable impact on the Thl/Th2 balance, and further discloses complete cellular and functional resolution of these effects by post treatment day 17. Cochran discloses substantial differences in the cellular and functional responses when compared to the present invention, responses which Applicants submit go to the very underpinnings of the present inventive methods. According to Cochran, the LPS treatment fails to disrupt the Thl/Th2 balance. Yet Cochran discloses that this balance is linked to the development of asthma and may be offset in subjects exposed to a nonmicrobial environment. Hence, in order to confer protection against the development of asthma, Cochran seeks to disrupt this balance, yet fails to disclose the sought after result (Cochran, page 274, first column). Generally, Th-1 represents a cellular response while Th-2 represents a humoral response, the former being more implicated in eliciting adaptations in the immune system and the latter reflecting operation of an existing adaptive response, for example, an allergic response. The balance between these operations is understood in the art as critical components of immune memory and the adaptive immune response in general. Implication of the Th-1 response is necessary to success in decreasing development of asthma while implication of the Th-2 system during this period is sought to be minimized. However, a successfully adapted Th-2 response exists in a subject protected from development of allergic asthma. Cochran, while noting that the decreased airway responsiveness to Mch in LPS- treated subjects is "apparently" supportive of the protective effect theory, notes its own deficiencies with respect to establishing an actual protective effect or forming the basis of an efficacious treatment method, stating "The protective effect of endotoxin on allergic response has not been invariably demonstrated [by these studies]... [and]... further studies [are] warranted to define these interactions" (page 274, second column, bottom of page).

The secondary reference, Previte, fails to overcome the deficiencies of the primary references or to otherwise suggest the present inventive methods. Further, Applicants submit that Previte stands for exactly

the opposite "safety" and "antigenicity" contentions as those put forth by the Examiner and fails to suggest or enable the instant invention. Applicants note that Previte is a 40+ year old reference with results that suggest an untenably high fatality rate among the IR-LPS treated subjects and an undesirable decrease in antigenicity upon irradiation in accordance with the Previte methods.

First, Applicants note that the Examiner's assertion that the IR-LPS of Previte could be safely imported into the methods of Cochran is unsupported and fails to consider the "relative" language/position of Previte. Although Previte reports a decrease in toxicity in bacterially derived LPS in general, lethality is still demonstrably higher than what would be considered acceptable in a treatment or prophylactic protocol. Further, the overall decrease in toxicity, according to Previte, is inconsistent across bacterial species. In particular, for E.coli LPS which Previte discloses as exhibiting the highest loss of toxicity upon irradiation, a 10% retention of toxicity after 20 Mrad is disclosed (see Figure 1, page 1610). Applicants note that 20 Mrad exceeds the top of the range recited in instant claim 2.

Second, the Examiner asserts that the IR-LPS of Previte retained antigenicity and therefore "stimulated the Th-1 arm of an animal's immune system in accordance with the present methods." Applicants submit first that this is an unsubstantiated and erroneous "if-then" relationship as there is no one-to-one correspondence understood in the art to exist between antigenicity in general, and stimulation of the Th-1 arm of an animals immune system specifically, although there is significant correlation. Regardless, Applicants submit that this statement is an erroneous interpretation of Previte. Applicants note that Previte actually discloses a startling decrease in antigenicity (see page 1611, top of page comparing LPS, 5 Mrad-LPS, and 20 Mrad-LPS, where mean survival times (scope of protection of vaccination) decreased respectively, and where "when six days elapsed between vaccination and challenge, the decrease in antigenicity caused by radiation was more evident." See also, page 1611, second column "The data recorded 21 days after challenge likewise indicated more extensive inactivation of antigenic components with increasing radiation dose" ). Applicants note that Previte is more absolute in his conclusory statements, using terms like "complete elimination" to describe impact on toxicity and "slight decrease" to describe antigenicity," but assert that this reflects a relative posture in comparison to previous data cited in Previte, and also is disclosed to reflect results at the most extreme Mrad endpoint of 20 Mrad, outside the scope of the instant invention.

Previte further teaches that the conditions of irradiation, including temperature and opportunity for free radical formation/presence of water are all factors which may cause significant variance in results (see page 1613, top of first column) so that one IR-LPS is not necessarily equivalent to another on a reference by reference basis. Finally, Previte hypothesizes that the difference in impact on antigenicity over time may be explained because "Radiation may leave specific determinants intact, allowing LPS to elicit the release of 'natural antibodies' and thus increase 'nonspecific resistance'...while more effectively destroying those responsible for 'specific antibody production (measured by protection after challenge at 6 days postvaccination)" and suggests further research to elucidate (see page 1613, bottom of first column). Applicants note that the results of Previte are not directly applicable nor do they predict results with respect to IR-LPS in general since Previte administers IR-LPS to adult subjects and is not concerned with effects or differences with respect to a developing immune system.

In addition to the fact that the results derived from the IR-LPS of Previte would not suggest the functioning of IR-LPS in accordance with the present invention, Previte fails to teach or suggest any relationship to or enhanced efficacy of LPS with respect to decreasing development of allergic asthma by virtue of the irradiation, as presently discovered, disclosed and exploited by the present inventive methods. Previte administers IR-LPS directly to adult mammals. The present specification teaches that the effect of exposure to LPS and IR-LPS (or any potential allergen) is different in the developing immune system versus the adult immune system and this difference is critical to the instant methods.

Due to the substantial safety issues remaining with even the 20 Mrad IR-LPS of Previte, Applicants submit that a person of ordinary skill in the art would not be guided by the Previte disclosure to import the IR-LPS of Previte into the experimental protocols of Cochran to achieve the instant invention,

which is primarily prophylactic in utility. Further, due to the Previte express suggestion that the components of antigenicity relating to adaptation of the immune system for response to future challenges are "destroyed" by irradiation, a person of ordinary skill in the art would be discouraged from the use of IR-LPS specifically to effectuate the long term protective effects and decrease in asthma targeted by the present invention. Finally, assuming arguendo that a person of ordinary skill in the art did import the IR-LPS of Previte into the protocols of the primary references, this still would not overcome the deficiencies noted above, that is, the different time frames for application and the different mode of application, both of which are critical to the efficacy of the present inventive methods.

Applicants submit that the Examiner's assertion that the functional characteristics of IR-LPS recited in the instant claims are inherent to IR-LPS barring specific data demonstrating a difference is actually inapposite to the patentability of the instant methods over these references. As to the merits of the assertion, Applicants note that even Cochran suggests an interplay in effectuated response relating to age of exposure, and Khan notes interplay with the dose of radiation, while the present inventors further recognize the importance the exposure time frame in terms of duration and the exposure via a particular route, all of which impact the response of the immunes system, so that there is no "inherency" with respect to a given active without multiple other controls being instigated.

Without regard to the merits of this assertion, Applicants note that recognition of an inherent characteristic and exploitation of that previously unrecognized characteristic in a method may confer patentability to that method, regardless of inherency. So, for example, if IR-LPS is "operable to stimulate the Th-1 arm" of the immune system without substantially impacting the Th-2 arm, this permits application of IR-LPS to an environment shared by both immature and mature mammalian species, so that the developing immune system of the former may be positively impacted while the developed and perhaps sensitive immune system of the latter would not be negatively impacted. A person of ordinary skill in the art, in the absence of this insight provided by the present disclosure, would not be guided toward such a method, even with awareness of IR-LPS, per se.

Applicants note once again that none of the cited prior art teaches or suggests that irradiated LPS derived from extracted bacterial endotoxin has Th 1 stimulating properties, especially with attenuated IL-1 stimulating properties, and with reduced Th 2 stimulating properties, compared to native LPS (see Declaration, Dr. Sipka, submitted October 2007), a recognition that would be necessary to be guided to realization of the instant inventive methods.

To establish prima facie obviousness of the claimed invention, all the claim limitations must be taught or suggested by the prior art, *In re Royka,* 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974). In order to render a claimed invention obvious, the prior art must enable one skilled in the art to make and use the claimed invention, *Motorola, Inc. v. Interdigital Tech. Corp.,* 43 U.S.P.Q.2d 1481, 1489 (Fed. Cir. 1997). Cochran fails to teach or suggest a method comprising *more than a single treatment* with non-irradiated LPS applied directly to the subject, whereas the present independent claims require a duration of exposure by, e.g. repeated administration across a maturation period of the subject with application to the subject's living environment. While Cochran posits that certain data "appears" consistent with the original hypothesis that LPS confers a protective effect against allergic asthma, Cochran admits that the actual results fail to yield a disruption in the Thl/Th2 balance, a disruption that Cochran teaches is implicated in restoring a normal Thl/Th2 balance to protect against the development of asthma. The secondary reference, Previte, which teaches single doses of IR-LPS to adult subjects to investigate the relationship between irradiation and retention of lethality and antigenicity, fails to overcome the deficiencies of Cochran, and, in fact, teaches that components of antigenicity relating to long term adaptations of the immune system (such as that which would be necessary to protect against development of asthma) may be destroyed by the levels of radiation needed for sufficient detoxification. There is no motivation in either reference to combine the teachings, since Previte is directed to treatment of adult subjects and teaches retention of an unacceptable degree of toxicity for medical uses, and further teaches against uses of IR-LSP for eliciting an adaptive immune response. Finally, importation of the IR-LPS of Previte into the Cochran protocol still fails to

enable the present methods, which require exposure during a maturation period of the developing mammal and exposure by application to the environment of the mammal."

It is the Examiner's position that Cochran need not demonstrate results which demonstrate a disruption in the Thl/Th2 balance, as alleged by Applicant. Cochran discloses a resulting airway hyperresponsiveness that results in a decrease in airway response to an allergen, upon administration of LPS to developing mice. The reference need not teach prevention or permanent efficacious treatment for airway hyperresponsiveness in order to be used as a reference. Contrary to Applicant's assertion, the lack of complete prevention of hyperresponsiveness does not "teach away" from the instant invention.

It is the Examiner's position that Applicant's argument that the Cochran disclosure is no more than basic science without any established utility, that there is no disclosure of a relevant method, that the difference between the basic science protocol disclosed by Cochran and the present inventive processes are many, many inventive steps apart in both sophistication and real world utility, and that these express "step" element differences confer substantial and patentable differences in the functioning of the respective methods is unpersuasive. The reference is being relied on for its specific teachings, namely the administration of LPS to neonatal or immature mammals to decrease development of allergic asthma.

It is the Examiner's position that Applicant's argument that "Previte stands for exactly the opposite "safety" and "antigenicity" contentions as those put forth by the Examiner" is unpersuasive. Applicant's assertions that "lethality is still demonstrably higher than what would be considered acceptable in a treatment or prophylactic protocol" and that Previte teaches "an

unacceptable degree of toxicity for medical uses" is unpersuasive because for purposes of the instant rejection what is or is not an "acceptable" degree of toxicity is not for Applicant to decide, nor is it a matter of what standards are presently medically acceptable for humans in the United States. The arguments of counsel cannot take the place of evidence in the record. In re Schulze , 145 USPQ 716, 718 (CCPA 1965). See MPEP 716.01 The reference teaches that toxicity is decreased and that teaching alone provides motivation to use irradiated LPS in place of LPS. It is noted that LPS is fully toxic and is being used medically in both the Previte et al. and Cochran et al. references.

Further, it is the Examiner's position that if the instant claims are enabled, so is the prior art. If irradiated LPS stimulates the Th1 arm of the animal's immune system in accordance with the present methods, then it would function in the same manner in the prior art. The motivation to use irradiated LPS over LPS has to do with decreased toxicity. The stimulation of the Th1 arm of the animal's immune system is inherent in using the irradiated LPS.

Applicant's assertion regarding the "relative" nature of the language in Previte et al., though not relevant, supports the Examiner's position. For example, Applicant argues "Previte is more absolute in his conclusory statements, using terms like "complete elimination" to describe impact on toxicity and "slight decrease" to describe antigenicity," but assert that this reflects a relative posture in comparison to previous data cited in Previte, and also is disclosed to reflect results at the most extreme Mrad endpoint of 20 Mrad, outside the scope of the instant invention." The language used in Previte is irrelevant. The reference is being used because it teaches that irradiated LPS is less toxic, not because it is antigenic. The reference teaches that irradiated LPS is slightly less antigenic and that does not preclude its use in the claimed

invention. The facts that Previte administers IR-LPS to adult subjects and not neonates and does not contemplate use in asthma are also not relevant and not necessary to make the instant rejection.

The Examiner agrees with Applicant in that "Applicants note that even Cochran suggests an interplay in effectuated response relating to age of exposure, and Khan notes interplay with the dose of radiation." Therefore, the references themselves are evidence that dosage and general treatment parameters are within the purview of those of ordinary skill in the art.

The Examiner also agrees with Applicant's argument that "Applicants note that recognition of an inherent characteristic and exploitation of that previously unrecognized characteristic in a method may confer patentability to that method, regardless of inherency." in some cases. However, in the instant case, the same patient population is receiving the same compound, so the results are necessary inherent.

It is noted that Applicant's assert evidence of an unpredicted and heretofore unknown differential impact of IR-LPS over LPS. However, such evidence has not been brought forth in the instant application that is commensurate in scope with the claims.

Accordingly, the rejection stands for reasons of record.

7. Claims 1-3, 5, 10, 13, 17-18 and 22-25 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Khan et al. (PTO-892 mailed on 01/29/2008, Reference V) in view of Previte et al. (PTO-892 mailed on 05/16/2007, Reference W) for the same reasons as set forth in the Office Action mailed on 01/29/2008.

Khan et al. teaches:

A process for decreasing development of allergic asthma (OVA induced asthma) comprising exposing an infant, neonatal or immature mammal maturing in an overly sterile environment shortly after birth (3 week old laboratory mice) to lipopolysaccharide derived from extracted bacterial endotoxin (LPS) by administering an aerosol spray composition of the mammal to a living environment/space (saline and air during intratracheal aspiration) during maturation of the mammal (at 3 weeks) (In particular, abstract).

Khan et al. teaches "recent evidence has suggested that post-natal exposure to endotoxin may protect against the development of allergen sensitization and asthma"(In particular, abstract).

The claimed invention differs from the prior art by the recitations of:

"irradiation detoxified lipopolysaccharide" in claims 1-3, 5, 10, 13, 17-18, 22-25;

"wherein exposure comprises at least weekly administration during maturation of the mammal" of claim 1;

"wherein the irradiation-detoxified lipopolysaccharide is detoxified by exposure of the endotoxin to irradiation at a level of from about 25 to about 150 kGy" in claim 2;

"wherein the irradiation changes the structure of the endotoxin while maintaining its Th1 stimulatory positive immune effect in the resulting irradiation-detoxified lipopolysaccharide" in claim 3;

"wherein the mammal is a human and during maturation is between 1 month and 2 years of age" of claim 13;

""during maturation" is throughout the maturing life cycle of the mammal" of claim 17;

"wherein administration is on a daily basis" of claim 18;

"wherein the mammal is a human infant and exposure comprises at least weekly administration from 1 month to 2 years of age" of claim 24; and

exposing a "human of up to about 2 years of age" and "wherein exposure comprises administration on an at least weekly basis of an aerosol spray composition comprising the irraditation-detoxified lipopolysaccharide at a concentration of 5-15 μg/ml" in claim 25.

Previte et al. teaches the detoxification of isolated LPS of S. typhimurium, S. enteritidis and E. coli using 4, 4.8 and 4.5 Mrad (about 25 to about 150 kGy) ionizing radiation. The detoxification eliminates lethality induced by its lethal determinants (changes the structure),

while retainining antigenticity (maintaining its Th1 stimulatory effect ) and pyrogenicity (In particular, abstract, whole document).

The functional limitations of The recitation of "operable to stimulate the Th1 arm of the human's immune system" of claims 1 and 22; and "operable to stimulate the Th1 arm of the human's immune system while reducing interleukin 1 (IL-1) stimulation caused by the native form of the lipopolysaccharide derived from extracted bacterial endotoxin" of claim 25; and "by restoring normal immune system development" in claim 22 are inherent properties of the reference irradiation-detoxified lipopolysaccharide. Where the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may be an inherent characteristic of the prior art, it has the authority to require the applicant to prove that the subject matter shown in the prior art does not possess the characteristics relied on. In re Schreiber, 44 USPQ2d 1429 (Fed. Cir. 1997).

It is noted that the specification does not provide a limiting definition for the term "living environment" and "living space" Therefore, the terms apply to all things that are in a "living environment" or "living space" including saline and air.

Claims 1-3, 5, 10, 13, 17-19, 22-25 are included because it would be conventional and within the preview of those skilled in the art to identify and determine the optimal modes, doses and frequency of administration. It has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill

in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

Khan et al. teaches "recent evidence has suggested that post-natal exposure to endotoxin may protect against the development of allergen sensitization and asthma"(In particular, abstract), it would have been obvious to one of ordinary skill in the art at the time the invention was made to practice the process taught by Khan et al in humans of 1 month to 2 years of age and during maturation. Khan et al. suggests performing the process for decreasing development of allergic asthma in young post-natal children implicitly.

One of ordinary skill in the art would have been motivated to use the irradiation detoxified lipopolysaccharide of Previte et al. in process for decreasing allergic asthma of Khan et al. because the process should be safe and without toxic effects for use in infants and children. Previte et al. teaches that LPS can be irradiation-detoxified of its lethal determinants while still retaining antigenicity and pyrogenicity. Therefore, it is obvious to use a safer, less toxic form of LPS in neonatal or immature mammals to decrease allergic asthma.

From the reference teachings, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

Applicant's arguments filed on 06/27/2008 have been fully considered, but are not found persuasive.

Applicant argues:

> ".. Khan specifically notes that treatment with LPS did not affect allergen-induced airway hyperresponsiveness (AHR), and concludes that "airway exposure to LPS produces transient AHR and inflammation in developing mice and does not appear to influence functional and immune responses induced by subsequent allergen sensitization" (see Poster Board 219). (Applicants further draw attention to the fact that Cochran and Khan are part of the same investigative team and yet publish opposing findings in the same publication year regarding impact on subsequent allergen sensitization.)
>
> Khan, therefore, exhibits the same deficiencies as Cochran (set forth in detail above) with respect to the missing elements defining the inventive methods, and expressly teaches away from the present methods by re-phrasing the more conservative and circumscribed conclusions of Cochran regarding "support" but lack of "invariable" evidence, into a more express teaching that LPS does not appear to influence the very responses sought to be elicited by the instant invention. Previte, as noted above, is directed to studying the efficiency of ionizing radiation in detoxifying the lethal determinant of LPS of various bacterial species and fails to teach or suggest the immunostimulatory properties of irradiated LPS that underpin the instant inventive methods. Not only is there an absence of any express or implied motivation to combine these references, Previte provides secondary evidence of nonobviousness by suggesting that the level of irradiation necessary to effectively detoxify LPS results in destruction of the components of antigenicity that may be related to eliciting a long term adaptive immune response. Hence, a person of ordinary skill in the art seeking methods to decrease development of allergic asthma would be discouraged from employing the IR-LPS of Previte into the protocols of Cochran or Khan. There must be a teaching or suggestion within the prior art, within the nature of the problem to be solved, or within the general knowledge of a person of ordinary skill in the field of the invention, to look to particular sources, to select particular elements, and to combine them as combined by the inventor. *See Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 665, 57 USPQ2d 1161, 1167 (Fed. Cir. 2000). "

It is the Examiner's position that Khan need not demonstrate results which demonstrate effective treatment, as alleged by Applicant. The reference need not teach prevention or permanent efficacious treatment for airway hyperresponsiveness in order to be used as a reference. Contrary to Applicant's assertion, the lack of complete prevention or treatment of hyperresponsiveness does not "teach away" from the instant invention. The reference is being relied on for its specific teachings, namely the administration of LPS to neonatal or immature mammals to decrease development of allergic asthma.

It is the Examiner's position that Applicant's argument that "Previte stands for exactly the opposite "safety" and "antigenicity" contentions as those put forth by the Examiner" is unpersuasive. Applicant's assertions that "lethality is still demonstrably higher than what would be considered acceptable in a treatment or prophylactic protocol" and that Previte teaches "an unacceptable degree of toxicity for medical uses" is unpersuasive because for purposes of the instant rejection what is or is not an "acceptable" degree of toxicity is not for Applicant to decide, nor is it a matter of what standards are presently medically acceptable for humans in the United States. The reference teaches that toxicity is decreased and that teaching alone provides motivation to use irradiated LPS in place of LPS. It is noted that LPS is fully toxic and is being used medically in both the Previte et al. and Cochran et al. references.

Further, it is the Examiner's position that if the instant claims are enabled, so is the prior art. If irradiated LPS stimulates the Th1 arm of the animal's immune system in accordance with the present methods, then it would function in the same manner in the prior art. The motivation to use irradiated LPS over LPS has to do with decreased toxicity. The stimulation of the Th1 arm of the animal's immune system is inherent in using the irradiated LPS.

Applicant's assertion regarding the "relative" nature of the language in Previte et al., though not relevant, supports the Examiner's position. For example, Applicant argues "Previte is more absolute in his conclusory statements, using terms like "complete elimination" to describe impact on toxicity and "slight decrease" to describe antigenicity," but assert that this reflects a relative posture in comparison to previous data cited in Previte, and also is disclosed to reflect results at the most extreme Mrad endpoint of 20 Mrad, outside the scope of the instant invention." The language used in Previte is irrelevant. The reference is being used because it

teaches that irradiated LPS is less toxic, not because it is antigenic. The reference teaches that irradiated LPS is slightly less antigenic and that does not preclude its use in the claimed invention. The facts that Previte administers IR-LPS to adult subjects and not neonates and does not contemplate use in asthma are also not relevant and not necessary to make the instant rejection.

One of ordinary skill in the art would have been motivated to use the irradiation detoxified lipopolysaccharide of Previte et al. in process for decreasing allergic asthma of Khan et al. because the process should be safe and without toxic effects for use in infants and children. Previte et al. teaches that LPS can be irradiation-detoxified of its lethal determinants while still retaining antigenicity and pyrogenicity. Therefore, it is obvious to use a safer, less toxic form of LPS in neonatal or immature mammals to decrease allergic asthma.

Accordingly, the rejection stands for reasons of record.

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nora M. Rooney whose telephone number is (571) 272-9937. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on (571)

272-0878. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

September 24, 2008
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